

Guest Editorial

Thyroid Toxicology and Brain Development: Should We Think Differently?

Thyroid hormone (TH) is essential for normal brain development. The simplicity of this statement, however, dramatically understates the complexity of the issues confronting us as we develop ways to identify factors in the environment that affect TH signaling in the developing brain, and methods of estimating the potential risk to human health of exposures to these factors. There are many known thyroid toxicants (Brucker-Davis 1998), and each has been identified solely by its ability to reduce circulating TH levels. Yet, we do not know the extent to which TH levels must decline before brain development is compromised. In addition, if there are chemicals in the environment that directly interfere with TH action on their receptors but do not affect TH levels in the blood, they cannot be identified as thyroid toxicants by the current screening methods. These two issues have been the focus of several recent reports, and the implications of their findings may change the way we think about thyroid toxicology.

Few experimental studies have modeled the effect of subtle TH insufficiency on brain development, but one group has begun to investigate this issue because undiagnosed maternal hypothyroxinemia may be prevalent in the general population. Lavado-Autric et al. (2003) reported that subtle TH insufficiency in the pregnant rat disrupts the migration of neurons in the fetal cortex and hippocampus, leading to the presence of neurons in aberrant locations of the adult offspring's brain and "blurring" cortical layers. Thus, the developing brain is more sensitive to maternal TH insufficiency than originally believed.

The paucity of experimental studies designed to identify the most sensitive end points of TH action in the developing brain shows that there are no well characterized end points of TH action that can be immediately recruited into toxicologic studies. However, new studies using genetic models of TH insufficiency are providing new insight that will help remedy this problem. Thyroid hormone receptors (TRs) are nuclear proteins that regulate gene expression; there are two types of TRs— α and β —and there are several isoforms of each of these two types (Zhang and Lazar 2000). These TR isoforms exhibit selective spatial and temporal patterns of expression in the developing brain, and recent work employing genetic lines carrying targeted deletions of specific TRs is revealing that specific TR isoforms mediate TH actions on specific developmental events. For example, migration of cerebellar granule cells is affected by TH acting on TR α , whereas development of the cerebellar Purkinje cells is dependent upon TH acting on both TR α and TR β (Morte et al. 2002).

These studies map the time and place of TH action during brain development, and the specificity with which TR isoforms mediate TH actions on specific developmental events. In turn, this information will permit the development of end points of thyroid toxicity in the developing brain. The combination of different end points of thyroid toxicity, reflecting actions mediated through different receptors, will likely provide strong evidence of the specificity of toxicant effects on TH signaling in the developing brain much the same way that the uterotrophic or Hershberger assays provide information about the specificity of toxicant effects on sex steroid signaling.

Identification of specific end points of TH action in the developing brain will also allow us to test whether environmental factors can exert effects on TR function. Moriyama et al. (2002) reported that bisphenol A (BPA) can bind to the TR; as little as 10 μ M can act as an indirect antagonist. Specifically, BPA can inhibit the ability of TH to regulate gene expression by inhibiting the release of the co-repressor N-CoR from the TR. A second group independently



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reported that polyhalogenated derivatives of BPA, tetrabromo- and tetrachloro-BPA, can bind to the TR with higher affinity than BPA and can act as TR agonists *in vitro* (Kitamura et al. 2002). These studies represent

the first evidence that there are chemicals in the environment that may interfere with TH signaling by acting directly on the TR, rather than by inhibiting function of the thyroid gland.

Currently, strategies for identifying thyroid toxicants only include assays of thyroid function—serum hormone levels and thyroid histopathology (Daston et al. 2003). These strategies will not identify chemicals, such as BPA, that interfere with TH signaling without reducing hormone levels. The variety of chemicals that could act in this manner may be more extensive than is generally believed. For example, Iwasaki et al. (2002) recently reported that some hydroxylated polychlorinated biphenyls can interfere with TH-induced gene expression by the same indirect antagonism as shown for BPA. In addition, if environmental chemicals can selectively affect a particular TR isoform, they will exert effects on brain development that are not consistent with hypothyroidism per se, but will instead produce a mosaic of effects that would be impossible to interpret without understanding the complexity of TH action on brain development.

Because TH is essential for normal brain development, we must incorporate new insights about the temporal and spatial complexity of TH action on the developing brain into strategies to identify thyroid toxicants. Moreover, it is essential to empirically determine the degree to which the developing brain is sensitive to TH insufficiency.

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R. Thomas Zoeller's research is focused on understanding the role of thyroid hormone in brain development, with a special emphasis on the fetal cerebellar cortex, and on identifying the mechanisms by which environmental chemicals may interfere with thyroid hormone signaling.

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